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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/715,868	11/17/2003	Juan Arroyo	06132/075002	5599

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EXAMINER	
SALVOZA, M FRANCO G	
ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 04/21/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/715,868	ARROYO ET AL.	
	Examiner	Art Unit	
	M. Franco Salvoza	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *05 January 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13 and 15-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3,6,9-13,15-17,20,23,24,27,30,31,34,37-39 and 42* is/are rejected.

7)☒ Claim(s) *4, 5, 7, 8, 18, 19, 21, 22, 25, 26, 28, 29, 32, 33, 35, 36, 40, 41, 43, 44* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. Claim 14 has been canceled. New claims 15-44 have been added.

2. Claims 1-13, 15-44 are pending and under consideration.

Claim Objections

Claim 15 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 15 recites the nucleic acid molecule of claim 1, wherein said nucleic acid molecule comprises the genome of a chimeric flavivirus comprising the pre-membrane and envelope proteins of West Nile virus and the capsid and non-structural proteins of Yellow Fever virus or the complement thereof. This claim fails to further limit the nucleic acid molecule of claim 1, since it recites broader subject matter than the now amended claim 1.

Claim Rejections - 35 USC § 112

NEW

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 15 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 15 recites the nucleic acid molecule of claim 1, wherein said nucleic acid molecule comprises the genome of a chimeric flavivirus comprising the pre-membrane and envelope proteins of West Nile virus and the capsid and non-structural proteins of Yellow Fever virus or the complement thereof. It is not clear to what "the complement thereof" refers to. Appropriate correction is required.

Claim Rejections – 35 USC 112

WITHDRAWN

Claim 1 was rejected under 35 U.S.C. 112, 2nd paragraph for being indefinite and failing to indicate which protein comprises an attenuating mutation. Applicant amended the claim, and the rejection is withdrawn.

Claims 6-8 were rejected under 35 U.S.C. 112, 2nd paragraph for being indefinite for the use of the word "thereof." Applicant amended the claims to specify phenylalanine, valine and arginine, respectively, and the rejection is withdrawn.

Claim 14 was rejected under 35 U.S.C. 112, 2nd paragraph for being indefinite and failing to set forth any method steps. The claim has been canceled so the rejection is moot.

Claim Rejections – 35 USC 101

WITHDRAWN

Claim 14 was rejected under 35 U.S.C. 101 because the claimed recitation of a use without setting forth any steps results in an improper definition of a process.

Applicant canceled claim 14, so the rejection is moot.

Claim Rejections - 35 USC § 102

WITHDRAWN

Claims 1, 9-13 were rejected under 35 U.S.C. 102(e) as being anticipated by U.S. Patent 6,696,281 to Chambers et al., which had a filing date of Dec. 1, 1999 and an issue date of Feb. 24, 2004.

Claim 1 was amended to recite a nucleic acid molecule comprising sequences encoding the pre-membrane and envelope proteins of West Nile virus and the capsid and non-structural proteins of Yellow Fever virus, wherein said envelope protein comprises and attenuating mutation in a region selected from the group consisting of: amino acids 102-112, amino acids 311-321, and amino acids 435-445.

Applicant argues that the claims as amended now specify the presence of one or more mutations in particular regions of the West Nile virus envelope protein, which are not described or suggested in the '281 patent.

Applicant's arguments are considered and found persuasive. The rejection is withdrawn.

Double Patenting

WITHDRAWN

Claims 10-12 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 8 and 9 of U.S. Patent 6,878,372 to Monath et al.

Applicant argues that the amended claims now specify the presence of one or more mutations in particular regions of the West Nile envelope protein, which are not described or suggested in the '372 patent.

Applicant's arguments are considered and found persuasive, and the rejection is withdrawn.

Claim Rejections - 35 USC § 112

MAINTAINED

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-13 were rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for attenuating mutations at amino acids 107, 316 and 440, does not reasonably provide enablement for each and every attenuating mutation within the amended range of 102-112, 311-321 and 435-445.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Applicant posits now that the amended claims focus on a range of exemplified mutations, any testing of mutations in these regions would not require undue experimentation, and it can be reasonably expected that other effective mutations can be found in these regions without undue experimentation.

This rejection is withdrawn as to claims 2-8, but is extended to new claims 15 and 37. Applicant's arguments are considered but found unpersuasive. In making a determination as to whether an application has met the requirements for enablement under 35 U.S.C. 112 P 1, the courts have put forth a series of factors. See, In re Wands, 8 USPQ2d 1400, at 1404 (CAFC 1988) and Ex Parte Forman, 230 U.S.P.Q. 546 (BPAI 1986). The factors that may be considered include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. Id. While it is not essential that every factor be examined in detail, those factors deemed most relevant should be considered.

As indicated above, claims recited a nucleic acid molecule comprising sequences encoding the pre-membrane and envelope proteins of West Nile virus and the capsid and non-structural proteins of Yellow Fever virus, wherein said envelope protein comprises an attenuating mutation in a region selected from the group consisting of: amino acids 102-112, amino acids 311-321 and amino acids 435-445.

References reviewing the state of the art for these particular diseases indicate that only residue 107 significantly reduces virulence, while mutations at residues 316 and 440 also have recognizable attenuating properties (Arroyo et al. (2004) as cited in the previous Office Action). However, Arroyo et al. also indicates that a combination of said mutations contribute to neurovirulence (Id., Table 5, p. 12500).

Applicant's disclosure contains examples of results using attenuating mutations at positions 107, 138, 176, 280 and 316 and 440 (pages 3, 8, 9; Table 1) and less successful results

for mutations at 138, 176, and 280. However, no specific data is indicated at other point positions within the amended ranges such as 102-106, 108-112, 311-315, 317-321, or 435-439, 441-445. The disclosure does not sufficiently teach enough beyond those three attenuating mutations (107, 316, 440) to counter the teachings in the art. Applicant has not indicated a specific nexus relating to those envelope protein domains and specific amended ranges of amino acids to demonstrate why any amino acids within those ranges or combinations of them would be sufficiently enabled for attenuating properties in West Nile.

In view of the breadth of the claims, the lack of examples or guidance, and the fact that those in the art would not be able to determine without extensive experimentation how to use specific attenuating mutations in the amended ranges of envelope protein amino acids 102-112, 311-321 and 435-445, the application has not provided sufficient information to enable those in the art to practice the claimed invention without undue experimentation.

Therefore, claims 1, 9-13, 15 and 37 stand rejected.

Claim Rejections - 35 USC § 103

MAINTAINED

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-13 were rejected under 35 U.S.C. 103(a) as being unpatentable over Guirakoo et al., Poidinger et al., Yang et al., and Allison et al.

Applicant argues that none of the cited references describes or suggests a mutation in 311-321 or 435-445. Additionally, position 107 talks about TBE which is a distinct virus, and there is no indication in Allison et al. as to whether any viruses including this mutation would replicate at levels sufficient to induce an immune response or replicate too much, thus providing no reasonable expectation of success.

Applicant also argues that Guirakoo et al. describes a chimeric flavivirus of YF and JE, but not WNV; Poidinger et al. indicates relatedness but not that Allison et al. mutation would be effective in producing vaccine virus strain. Further, Allison et al. says 2 wild type viruses in references 30 and 6 contain phenylalanine at residue 107 to cause disease in humans and therefore teach away from including the amino acid at position 107.

Finally, applicant posits that Yang et al. teaches a DNA vaccine based on WN capsid protein, and the present invention does not pertain to DNA vaccines or use WN capsid proteins, rather the capsid sequences are derived from YF.

Applicant's argument in regard to positions 311-321 or 435-445 is persuasive, and the rejection is withdrawn as far as claims 4, 5, 7 and 8. However, applicant's other arguments are considered but found unpersuasive.

First, the 103(a) rejection is a *combination* of references (emphasis added). As explained in the previous Action, Guirakoo et al. was cited for the Yellow Fever backbone to deliver genes of other flaviviruses to be combined with envelope proteins from West Nile virus, a close relative of Japanese encephalitis virus, as taught by Poidinger et al.

Additionally, the Allison et al. reference refers to the attenuating mutation at position 107 of the flavivirus envelope protein, structurally common to flaviviruses: "The E proteins of all

mosquito- and tick-borne flaviviruses have at least 40% amino acid identity and their six intramolecular disulfide bridges are conserved, indicating a common overall structure" (p. 4268). While TBE is a distinct flavivirus, Allison et al. teaches that a mutation at position 107 would lead to functional changes without disrupting the native structure that is almost completely conserved among flaviviruses, except for Powassan virus, a specific strain of JEV and a specific dengue virus strain (p. 4270). Additionally, the recitation of Allison et al. to substitution of phenylalanine to leucine at position 107 is recited as a conservative substitution wherein the mutant still retained a significant degree of fusion activity and native structure which would enhance and not abolish the induction of an immune response (p. 4270).

Furthermore, as indicated in the previous Office Action, Yang et al. is recited to teach the induction of an immune response with West Nile capsid proteins. The claim recitation of "inducing an immune response" is interpreted broadly. The administration of an antigen, any antigen, is sufficient to induce even a minor immune response within the scope of the claim.

One of ordinary skill in the art would have had a reasonable expectation for success since Guirakoo et al. teaches that flaviviruses such as Japanese Encephalitis can be delivered on a Yellow Fever backbone and Poidinger et al. teaches that JEV is a close genetic relative of West Nile. Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made, absent unexpected results to the contrary.

The rejection is maintained for reasons of record.

The rejection applies to new claims 15, 16, 17, 20, 23, 24, 27, 30, 31, 34, 37, 38, 39, 42. Claims 15 recited the nucleic acid molecule of claim 1; claims 16, 17, 20, 22 recite the chimeric

flavivirus as in rejected claim 9; claims 23, 24, 27, 30, 31, 34 recite the method of inducing an immune response as in rejected claim 10; claims 34, 37, 38, 39, 42 recite a vaccine composition comprising the flavivirus of claim 9, interpreted as a composition comprising the rejected flavivirus of claim 9.

Double Patenting

NEW

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 10-12 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 8 and 9 of U.S. Patent No. 6, 878, 372 to Monath et al.

As the 103(a) obviousness rejection is maintained over the combination of references, so may the U.S. Patent 6, 878, 372 to Monath et al. still stand as a reference to be used in combination with the other references to render the invention obvious.

As indicated in the previous Action, the conflicting claims may not be identical, but they are not patentably distinct from each other because U.S. Patent No. 6, 878, 372 claims a method of preventing or treating West Nile virus infection, said method comprising administering a chimeric flavivirus comprising the capsid and non-structural proteins of a yellow fever virus and the pre-membrane and envelope West Nile virus. Applicant's claim 10 is rendered obvious under claim 1 of the Monath reference, since in both instances the chimeric flavivirus would be used in a method to induce an immune response to West Nile Virus in a subject.

Further, applicant claims in claim 11 that the subject is at risk of developing West Nile virus infection, which is obvious over Monath's claims 1 and 8, which recite a method of preventing West Nile virus infection in a subject that does not have it but is at risk of developing it. Finally, applicant's claim 12 is obvious over Monath's claims 1 and 9 drawn to the method of treating a subject already infected by West Nile virus.

This rejection also applies to new claims 23, 24, 27 that depend on rejection claim 10 and recite further limitations for said attenuating mutation.

Thus, claims 10-12, 23, 24, and 27 stand rejected under the judicially created doctrine of obviousness-type double patenting.

Conclusion

Claims 4, 5, 7, 8, 18, 19, 21, 22, 25, 26, 28, 29, 32, 33, 35, 36, 40, 41, 43, 44 are objected to for being dependent on a rejected claim. However, if rewritten the claims would be allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to M. Franco Salvoza whose telephone number is (571) 272-8410. The examiner can normally be reached on M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel can be reached on (571) 272-0902. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

M. Franco Salvoza
Patent Examiner
April 12, 2006

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